

CLINICAL RESEARCH**Interventional Cardiology**

Predictive Factors for Ischemic Target Vessel Revascularization in the Prevention of Restenosis With Tranilast and its Outcomes (PRESTO) Trial

Mandeep Singh, MD,* Bernard J. Gersh, MB, ChB, DPHIL,* Robyn L. McClelland, PhD,†
Kalon K. L. Ho, MD, MSc,‡ James T. Willerson, MD,§ William F. Penny, MD,||
David R. Holmes, Jr, MD*

Rochester, Minnesota; Boston, Massachusetts; Houston, Texas; and San Diego, California

OBJECTIVES	The aim of the present study was to determine the rates of target vessel revascularization (TVR) and to determine predictors of TVR from clinical and angiographic variables available in the Prevention of Restenosis With Tranilast and its Outcomes (PRESTO) database.
BACKGROUND	The rates of TVR after percutaneous revascularization procedures, and its prediction with available clinical and angiographic variables, is less well known.
METHODS	We studied nine-month TVR in 11,484 patients enrolled in the PRESTO trial. Clinical, lesion-related, and procedural characteristics were analyzed in a logistic regression model. Study data were divided at random into an 80% training set on which the models were developed and a 20% hold-out set on which the model properties were evaluated.
RESULTS	A total of 14% (n = 1,609) had ischemic TVR. Clinical variables with increased risk for TVR included younger age; hypertension; diabetes mellitus; nonsmokers; unstable angina; previous coronary artery bypass grafting; peripheral vascular disease; procedure- and lesion-related such as ostial location, multilesion angioplasty, location in the left anterior descending artery, length ≥ 20 mm, in-stent restenosis at baseline, and use of rotablator. There was significant increase in the risk of ischemic TVR at U.S. treatment sites. Smoking and stent placement were associated with lower risk of ischemic TVR. The mean area (\pm SD) under the receiver-operating characteristic curve of the bootstrap samples was 0.66, indicating a modest ability of the model to discriminate patients who needed TVR on follow-up.
CONCLUSIONS	Despite being the largest prospective trial designed to test restenosis, the discriminatory ability of the clinical and angiographic variables to predict TVR is modest. (J Am Coll Cardiol 2005;45:198–203) © 2005 by the American College of Cardiology Foundation

Previous clinical and angiographic studies of percutaneous coronary interventions (PCI) have consistently observed disparity in clinical and angiographic rates of restenosis, with higher rates of angiographic restenosis (1–4). Though angiographic assessment of restenosis helps in identifying the clinical and angiographic variables in its causation, the true measure of success or failure after PCI is determined, however, by the clinical events such as death, myocardial infarction, and target vessel revascularization (TVR) (1). In addition, derivation of information from pooled information from different trials and registries and inclusion of selected populations limits the generalizability of the results. The Prevention of Restenosis With Tranilast and its Outcomes (PRESTO) trial was designed to evaluate the effects of tranilast, an oral anti-inflammatory agent, on major adverse cardiovascular events and angiographic and intravascular end points (5). The PRESTO trial provided

important information on ischemic TVR in 11,484 patients. With this background, we sought to study the rates of ischemia-related TVR in the current interventional era. The second purpose of this retrospective analysis was to identify and predict the clinical and angiographic variables that increase the risk of ischemic TVR and to internally validate the predictors in the PRESTO trial.

METHODS

Study population. The PRESTO trial has been previously described (5). In brief, it was a double blind, placebo-controlled, parallel group study of patients after PCI. The primary end point was the first occurrence of major adverse cardiovascular events within nine months defined as death, myocardial infarction, and/or ischemia-driven TVR. Restenosis was defined as $\geq 50\%$ stenosis in the treated segment at follow-up, or at least 50% loss of the original gain in the minimal luminal diameter. Ischemia-driven TVR was defined as intervention for chest pain or a positive test for ischemia (exercise stress test, stress echocardiogram, 24-h Holter monitor, resting electrocardiographic evidence of ST-segment depression or elevation in >1 lead, or radio-nuclide study showing reversible defect). The type of inter-

From the *Division of Internal Medicine and Cardiovascular Diseases and †Division of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota; ‡Harvard Clinical Research Institute, Boston, Massachusetts; §Texas Heart Institute, Houston, Texas; and the ||University of California, San Diego, California. David J. Moliterno acted as guest editor on this article.

Manuscript received March 25, 2004; revised manuscript received May 10, 2004, accepted May 11, 2004.

Abbreviations and Acronyms

PCI	= percutaneous coronary intervention
PRESTO	= Prevention of Restenosis With Tranilast and its Outcomes trial
ROC	= receiver-operating characteristic
TVR	= target vessel revascularization

vention performed was at the investigators discretion, with the exclusion of intracoronary radiation.

Statistical analysis. Summary data are expressed as the mean value \pm SD or as a percentage. Unadjusted comparisons between those who developed ischemic TVR within nine months and those who did not were performed with chi-square tests for categorical patient or lesion characteristics, and two-sample *t* tests for continuous variables. Baseline demographic, patient characteristics, angiographic, and procedural variables were screened univariately using a <0.05 level of significance. Standard stepwise procedures were then used to select variables to include in the final multivariable model. A two-tailed *p* value ≤ 0.05 was considered significant. A multiple logistic regression model was constructed with the following variables considered as candidates: age, Caucasian race, study center, gender, hypertension, treated diabetes mellitus (oral agent or insulin), smoking status, previous coronary artery bypass surgery, previous PCI, dyslipidemia, history of congestive heart failure, current unstable angina, peripheral vascular disease, American College of Cardiology/American Heart Associa-

tion type C lesion, and lesion characteristics ([length >20 mm], bifurcation, ostial, in-stent restenosis, restenotic, diffuse, discrete, pre-PCI stenosis, use of intracoronary stent, rotablator, vessel treated [left anterior descending vs. others], lesions treated [single vs. multiple]).

The model's goodness-of-fit was assessed using the Hosmer-Lemeshow method. Model discrimination was assessed using the area under the receiver-operating characteristic (ROC) curve or the *c*-statistic. Study data were divided at random into an 80% training set on which the models were developed, and a 20% hold-out set on which the model properties such as the area under the ROC curve were evaluated. The risk score was calculated for each patient and the area under the ROC curve was determined for each sample. To study the performance of the variables on patient subgroups, the data were stratified according to de novo lesions and adjusted for whether they received the stent.

RESULTS

Baseline characteristics. A total of 11,484 patients were enrolled in the PRESTO trial. Ischemia-driven TVR was noted in 1,609 patients (14%). The baseline characteristics of patients who required ischemic TVR and those who did not (*n* = 9,875) are shown in Table 1. Among other characteristics, female gender, nonsmoker, hypertension, treated diabetes mellitus, hyperlipidemia, history of percutaneous or surgical revascularization, congestive heart failure, acute coronary syndrome, and peripheral vascular disease were associated with higher incidence of ischemic TVR.

Table 1. Baseline Clinical Characteristics of Patients With and Without TVR

	TVR Event (<i>n</i> = 1,609)	No TVR Event (<i>n</i> = 9,875)	<i>p</i> Value
Age (yrs)	59.9 \pm 10.5	60.3 \pm 10.4	0.21
Male, <i>n</i> (%)	1,200 (75)	7,693 (78)	0.003
Tranilast treatment, <i>n</i> (%)	1,285 (80)	7,901 (80)	0.89
Treatment center, <i>n</i> (%)			< 0.001
United Kingdom, West Europe, South Africa	534 (33)	4,321 (44)	
U.S.	929 (58)	4,097 (42)	
Other	141 (9)	1,401 (14)	
Medical history, <i>n</i> (%)			
Current smoker	297 (18)	2,299 (23)	< 0.001
Hypertension	1,107 (69)	5,904 (60)	< 0.001
Diabetes mellitus	480 (30)	2,204 (22)	< 0.001
Dyslipidemia	1,103 (69)	6,343 (64)	< 0.001
Previous myocardial infarction	625 (39)	3,828 (39)	0.94
Previous coronary bypass surgery	313 (19)	1,248 (13)	< 0.001
Previous percutaneous interventions	707 (44)	2,844 (29)	< 0.001
History of congestive heart failure	127 (8)	569 (6)	< 0.001
History of coronary artery disease	975 (61)	5,407 (55)	< 0.001
History of acute coronary syndrome	1,115 (69)	5,680 (58)	< 0.001
Peripheral vascular disease	131 (8)	548 (6)	< 0.001
Cerebrovascular accidents	68 (4)	315 (3)	0.031
History of stable angina	334 (21)	1,532 (16)	< 0.001
Previous unstable angina	603 (38)	2,873 (29)	< 0.001
Current stable angina	571 (35)	4,154 (42)	< 0.001
Current unstable angina	988 (62)	4,898 (50)	< 0.001
Statins	1,264 (79)	7,128 (72)	< 0.001

TVR = target vessel revascularization.

Table 2. Lesion Characteristics of Patients With and Without TVR

	TVR Event (n = 1,609)	No TVR Event (n = 9,874)	p Value
Lesion length, n (%)			< 0.001
<10 mm	422 (27)	3,052 (31)	
10–20 mm	909 (57)	5,670 (58)	
>20 mm	260 (16)	1,063 (11)	
Pre-PCI stenosis	88.2 ± 9.8	87.2 ± 10.4	< 0.001
Post-PCI stenosis	6.7 ± 11.1	5.2 ± 9.8	< 0.001
PCI procedure, n (%)			
Balloon dilation	1,596 (99)	9,784 (99)	0.49
Rotablator	137 (9)	321 (3)	< 0.001
Stent	1,120 (70)	7,947 (81)	< 0.001
Lesion characteristics, n (%)			
Angulated >45°	130 (8)	848 (9)	0.50
Bifurcated	191 (12)	966 (10)	0.010
Calcified	255 (16)	1,540 (16)	0.79
De novo	1,188 (74)	8,643 (88)	< 0.001
Diffuse disease	406 (25)	1,929 (20)	< 0.001
Discrete	376 (23)	2,598 (26)	0.013
Eccentric	769 (48)	4,777 (48)	0.67
In-stent restenosis	361 (22)	931 (9)	< 0.001
Irregular	418 (26)	3,038 (31)	< 0.001
Ostial	194 (12)	652 (7)	< 0.001
Restenotic	418 (26)	1,229 (12)	< 0.001
Total occlusion	150 (9)	867 (9)	0.47
Lesion characteristics, n (%)			
Lesion length (mm)	15.2 ± 11.0	13.3 ± 8.5	< 0.001
Lesion type, n (%)			< 0.001
A, B1, B2	1,263 (79)	8,284 (84)	
C	343 (21)	1,576 (16)	
Vessels treated, n (%)			< 0.001
Left anterior descending	611 (38)	3,629 (37)	
Right coronary artery	466 (29)	3,309 (34)	
Circumflex	402 (25)	2,387 (24)	
Other	129 (8)	549 (6)	
Lesions per patient	1.6 ± 0.7 (n = 803)	1.4 ± 0.7 (n = 5,119)	< 0.001
Ejection fraction (%)	59.5 ± 12.0	60.3 ± 12.4	0.07

PCI = percutaneous coronary interventions; TVR = target vessel revascularization; type A, B1, B2, and C = American College of Cardiology/American Heart Association classification.

Table 2 highlights the angiographic features of patients with and without ischemic TVR. Longer lesion length (>20 mm), tighter preprocedure stenosis, higher residual stenosis, and use of rotablator were associated with higher incidence of ischemic TVR. The lesion characteristics associated with higher TVR were bifurcation, ostial, diffuse, restenotic lesions, or lesions with in-stent restenosis.

Multivariable correlates. Stepwise regression modeling results of the variables associated with significantly increased risk of ischemic TVR are presented in **Table 3**. The significant independent predictors of TVR in this study are age, treatment site (U.S.), nonsmoker, hypertension, treated diabetes mellitus, peripheral vascular disease, previous coronary artery bypass surgery, and current unstable angina. Among the angiographic predictors, lesion length >20 mm, ostial location, angioplasty of left anterior descending artery, multivessel angioplasty, and use of rotablator were associated with a higher incidence of ischemic TVR. The data did not deviate significantly from the logistic model, as indicated by the nonsignificant Hosmer-Lemeshow test result

($p = 0.1285$). The mean area (\pm SD) under the ROC curve of the bootstrap samples was $0.66 (\pm 0.03)$, indicating a fair ability to discriminate between patients who required TVR during follow-up and those who did not.

Validation set. Results from fitting the same model used for the whole (training) set to the subset with de novo lesions adjusted for intracoronary stents are displayed in **Table 4**. The predictors of ischemic TVR in this subgroup were similar to the overall group of patients treated for ischemic TVR. Area under the ROC curve for the prediction model applied to the hold-out sample of 2,297 patients was 0.64 (95% confidence interval 0.60 to 0.67), indicating modest ability to discriminate in this subset of patients with de novo lesions.

DISCUSSION

The present study demonstrated several clinical and angiographic features that are associated with an increased risk of TVR after PCI. Younger age, hypertension, diabetes mel-

Table 3. Stepwise Multivariate Modeling Results of Overall Patients Enrolled in PRESTO Trial*

Effect	Odds Ratio	95% CI	p Value
Center: U.S. vs. other	1.365	(1.190–1.566)	< 0.0001
Age (yrs)	0.987	(0.981–0.993)	< 0.0001
Smoker	0.722	(0.611–0.853)	0.0001
Hypertension	1.232	(1.074–1.413)	0.0028
Diabetes: diet only or no treatment vs. no diabetes	1.088	(0.850–1.392)	0.5029
Diabetes: insulin and/or oral agent vs. no diabetes	1.530	(1.220–1.920)	0.0002
Diabetes: oral agent only vs. no diabetes	1.184	(1.184–1.425)	0.0748
Prior coronary artery bypass surgery	1.393	(1.180–1.644)	< 0.0001
Peripheral vascular disease	1.314	(1.035–1.667)	0.0249
Current unstable angina	1.446	(1.267–1.650)	< 0.0001
Lesion length: >20 mm vs. <20 mm	1.467	(1.233–1.745)	< 0.0001
In-stent restenosis lesion	2.050	(1.721–2.442)	< 0.0001
Ostial lesion	1.455	(1.185–1.787)	0.0003
Stent	0.840	(0.719–0.981)	0.0273
Vessel treated: LAD vs. other	1.260	(1.059–1.374)	0.0047
Number of lesions treated: single vs. multiple	0.580	(0.511–0.659)	< 0.0001
Rotablator	1.424	(1.097–1.848)	0.0079

*Hosmer and Lemeshow Goodness of Fit test: chi-square = 12.5456, degrees of freedom = 8, probability > chi-square = 0.1285.

CI = confidence interval; LAD = left anterior descending artery; PRESTO = Prevention of Restenosis with Tranilast and Its Outcomes trial.

litus, unstable angina, and previous CABG were among the clinical variables associated with higher risk of ischemic TVR. Ostial lesion location, multivessel angioplasty, lesion location in the left anterior descending artery, lesion length more than 20 mm, and use of rotablator were among the lesion- and procedure-related variables associated with ischemic TVR on follow-up. There was a significant increase in the risk of ischemic TVR at U.S. treatment sites. Smoking and the use of stents were associated with a lower risk of TVR.

The present study. The target vessel (lesion) revascularization rates have remained stable since the introduction of intracoronary stents. In the earlier Balloon-Expandable-Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease (Benestent) study, comparing balloon angioplasty with intracoronary stents in patients

with simple de novo lesions in the native coronary arteries, the seven-month all-event rate in the stent arm was 13.5% (6). In a more recent higher-risk group of multivessel disease in Arterial Revascularization Therapies Study (ARTS) group, the one-year repeat revascularization in the stent-treated group was 16.8% (7). Similarly, in the Sirolimus-Eluting Stents versus Standard-Stents in patients with in a native coronary artery (SIRIUS) trial, the target lesion revascularization at 270 days was 16.6% in the control (bare metal stent) group (8). In recent large pooled data from stent trials, the TVR rates were 14.3% in 6,186 patients (1). Despite worsening baseline and lesion characteristics, the repeat revascularization rates have been the same and ranged between 13% and 16%. The ischemic TVR of 14% in the present study is similar to the previously reported studies. The previously published data are, how-

Table 4. Stepwise Multivariable Modeling Results of De Novo Lesions Treated With Intracoronary Stents

Effect	Odds Ratio	95% CI	p Value
Center: U.S. vs. other	1.467	(1.259–1.709)	< 0.0001
Age	0.989	(0.982–0.996)	0.0033
Smoker	0.746	(0.620–0.897)	0.0018
Hypertension	1.225	(1.051–1.429)	0.0096
Diabetes: diet only or no treatment vs. no diabetes	1.098	(0.833–1.448)	0.5059
Diabetes: insulin and/or oral agent vs. no diabetes	1.421	(1.083–1.866)	0.0113
Diabetes: oral agent only vs. no diabetes	1.225	(0.991–1.515)	0.0612
Prior coronary artery bypass surgery	1.301	(1.068–1.585)	0.0090
Peripheral vascular disease	1.247	(0.941–1.653)	0.1247
Current unstable angina	1.389	(1.199–1.610)	< 0.0001
Lesion length: >20 mm vs. <20 mm	1.527	(1.246–1.872)	< 0.0001
Ostial lesion	1.339	(1.047–1.713)	0.0200
Stent	0.725	(0.603–0.872)	0.0006
Vessel treated: LAD vs. other	1.313	(1.134–1.520)	0.0003
Number of lesions treated: single vs. multiple	0.574	(0.498–0.663)	< 0.0001
Rotablator	1.436	(1.000–2.062)	0.0500

CI = confidence interval; LAD = left anterior descending artery.

ever, limited by single-center data, pooled data analysis from several registries and trials, or limiting the study to a specific subgroup. In a recent analysis of angiographic variables from Do Tirofiban and ReoPro Give Similar Efficacy Outcomes? (TARGET), the risk of six-month TVR was independently associated with left anterior descending coronary artery lesions (hazard ratio 1.46; $p < 0.001$), restenotic lesions at baseline (hazard ratio 1.58; $p = 0.006$), and lesion length (hazard ratio 1.19; $p = 0.03$) (9). In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, the triple composite of death, myocardial infarction, or TVR at 12 months was reduced from 22.1% in the placebo-treated patients to 17.5% with eptifibatide treatment (hazard ratio 0.76; 95% confidence interval 0.63 to 0.93; $p = 0.007$). Overall rates for TVR were greater in patients with diabetes (hazard ratio 1.59; 95% confidence interval 1.21 to 2.08; $p < 0.001$) (10).

In contrast, the data of this retrospective analysis were derived from a single, largest, prospective, multicenter, multinational trial with same primary end point (silent and symptomatic) TVR on follow-up. The patient population included lesion characteristics and the treatment offered; they are representative of current interventional practice and represent the “real-world” TVR rates.

The variables identified in the present study associated with increased risk for ischemic TVR have previously been reported with the notable addition of higher incidence of ischemic TVR in patients treated in the U.S. compared with patients treated in the other countries. The reason for higher ischemic TVR is not exactly known; however, higher prevalence of adverse baseline characteristics associated with restenosis, more aggressive invasive approach to patients’ symptoms (11,12), abnormalities noted in the stress test, or some unidentified factors in the U.S. population that can increase the restenosis and, consequently, the TVR could be the possible factors.

Predictors of ischemic TVR. As previously mentioned, the predictors of ischemic TVR were, in general, similar to restenosis (3,13–15). We did a subset analysis on patients with de novo lesions that received stents to analyze the predictors of ischemic TVR in a uniform population. The predictors identified in this subgroup were essentially similar to the overall population. However, the predictive accuracy of the models derived from PRESTO data, to differentiate between patients who would and who would not develop ischemic TVR, was modest. These data are in line with the previously published studies with low-to-modest predictive accuracy for prediction of restenosis and TVR (3,15,16). Target vessel size was not included as a predictor, as it was only available in the angiographic substudy of the trial. Despite inclusion of all the clinical, lesion-specific, and procedural variables, there may be some unmeasured patient, genetic, or lesion-specific variables that can account for the remainder (17–20). Until these unmeasured confounders are known, we may not be able to accurately predict the likelihood of a patient developing restenosis (and

ischemic TVR) after successful percutaneous revascularization. It would also be difficult to develop treatment algorithms (including drug-eluting stents) based on the available clinical, angiographic, and procedural data.

Study limitations. This large prospective study lacked the predictive accuracy to differentiate patients who needed TVR from a group that did not. Though this study is one of the largest and representative of the recent practice, many important subsets, namely vein grafts, bifurcation, left main disease that are known to have higher restenosis, were underrepresented. Also, other features believed to be associated with higher risk of repeat revascularization (e.g., chronic total occlusion, and patients with chronic renal failure) were underrepresented. Thus, these features could not be evaluated in the present study. The PRESTO trial did not include patients who received intracoronary brachytherapy or drug-eluting stents and, therefore, our analysis cannot be extrapolated to this subset. The predictors for TVR had only modest discriminatory accuracy with a c-statistic of 0.66. It is likely that some unmeasured variables are affecting restenosis and, consequently, repeat revascularization.

Conclusions. The TVR of 14% found in this study is representative of the “real-world” repeat revascularization rates with current patient demographics, lesion characteristics, and procedural techniques. These rates may serve as benchmark to compare the effect of newer strategies to reduce restenosis and TVR. The predictive accuracy of clinical and angiographic variables in TVR prediction is modest, and should serve as an impetus to search for newer markers for restenosis prediction.

Reprint requests and correspondence: Dr. David R. Holmes, Jr., Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, 200, 2nd Street SW, Rochester, Minnesota 55905. E-mail: holmes.david@mayo.edu.

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